REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Nonelected claims 3-6 are cancelled without prejudice to the filing of a divisional application thereon. Claims 1 and 2 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1 and 2 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while being enabling for two hyperthermostable protease enzymes comprising the amino acid sequence of SEQ ID NO:1 or 5, does not reasonably provide enablement for any functional equivalents (i.e., mutants and variants having the very same function of being a hyperthermostable protease). This rejection is respectfully traversed.

Claims 1 and 2 are amended to now recite that the functional equivalent of the hyperthermostable protease has the same amino acid sequence as SEQ ID NO:1 or 5, but with the exception that one amino acid residue to 5% of the amino acid residues of SEQ ID NO:1 or 5 are mutated. SEQ ID NO:5 is a hybrid hyperthermostable protease containing sequences from PFUS protease (SEQ ID NO:3) and TCES protease (SEQ ID NO:1).

A BLAST amino acid sequence alignment of SEQ ID NO:1 (TCES protease designated as sequence 1 in the alignment) and SEQ ID NO:3 (PFUS protease designated as sequence 2 in the alignment) disclosed in the instant application is attached hereto for the examiner's consideration. The calculated sequence homology is 78%, with homologous but not identical amino acid residues (i.e., Ile and Val) at particular positions indicated by the symbol "+" in the line between the aligned sequences. Furthermore, the specification at page 20, lines 8-17, teaches that there is extremely high homology around four amino acid residues (citing Protein Engineering, Volume 4, pages 719-737 (1991)), which are considered to be important for catalytic activity of the protease (see also Figures 11 and 12 of the instant application). These amino acid residues are:

SEQ ID NO:1	167D, 200H, 299N, 362S
SEQ ID NO:3	34D, 67H, 167N, 230S
SEQ ID NO:5	166D, 199H, 299N, 362S

as would be readily recognized and understood by one of skill in the art. This same person of skill in the art would furthermore understand that because of the importance of these residues for protease catalytic activity, it would be desirable not to introduce changes to these residues or to neighboring amino acid sequences. However, changes such as

substitution with conservative amino acid residues can safely be made of positions indicated by the symbol "+". In addition, amino acid substitutions of residue positions which are not conserved or homologous can also be made. Accordingly, one of skill in the art, based on the above information and the guidance in the specification, including the protease activity assay at pages 50-53 and the thermostability assay at pages 58-61, is fully enabled to make functional equivalents of the hyperthermostable proteases of SEQ ID NO:1 or 5 in which one residue up to 5% of the amino acid residues are mutated.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-2 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Claims 1 and 2 are now amended to recite that the functional equivalents of the hyperthermostable protease of SEQ ID NO:1 or 5 are those in which a single amino acid residue up to 5% of the amino acid residues are changed. The

USPTO's "Synopsis of Application of Written Description Guidelines" provides Example 14 (Product by Function) which teaches what would be required to satisfy the written description requirement for variants of a protein/enzyme, which variants have at least 95% sequence identity to SEQ ID NO:3 and catalyze the reaction of A to B. The analysis for this example teaches that the single disclosed species of SEQ ID NO:3 is representative of the genus because all members have at least 95% structured identify with the reference compound (SEQ ID NO:3) and because of the presence of an assay which applicant provided for identifying all of the at least 95% identified variants of SEQ ID NO:3 which are capable of the specified catalytic activity. The analysis of Example 14 concludes by stating the disclosure meets the written description requirements for a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A to B.

The presently claimed functional equivalent of a hyperthermostable protease has at least 95% sequence homology/identity to the hyperthermostable protease of SEQ ID NO:1 or 5, and the enzymatic activity and thermostability property can be readily assayed as disclosed in the specification at pages 50-53 and 58-61. Accordingly, the functional equivalents recited in the claims are adequately

described in the present specification and therefore satisfy the written description requirement.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-2 have been rejected under 35 U.S.C. §102(b) as being anticipated by Ilse et al. (Blumenthal et al.), *Appl. Environ. Microbiol.*, 56(7):1992-1998 (1994) or Morikowa et al., *Appl. Environ. Microbiol.*, 60(12):4559-1998 (1994). This rejection is respectfully traversed.

From the examiner's comments, the examiner appears to be indicating that it is only the functional equivalents recited in the present claims that are taken as reading on the enzymes of Ilse and Morikowa because there is no limitation placed on the number of changes that can be present in the polypeptide sequence of SEQ ID NO:1 or 5. Claims 1 and 2 are now amended to positively recite that, in the functional equivalents, there are only from a single residue to at most 5% of the amino acid residues that are changed from the sequences of SEQ ID NO:1 or 5. Accordingly, Ilse (Blumenthal) or Morikowa can not anticipate the presently claimed hyperthermostable protease of SEQ ID NO:1 or 5 or the recited functional equivalents thereof.

Furthermore, the presently claimed hyperthermostable protease is believed to be a serine protease because it is

inhibited by a typical serine protease inhibitor, PMSF, as disclosed on page 65, line 21, to page 67, line 20 and Table 1 of the present specification. By contrast, Morikowa's enzyme is a thiol protease which is not inhibited by PMSF as clearly shown in Table 2 on page 4564.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-2 have been rejected under 35 U.S.C. §101 as claiming the same invention as that of claim 1 of prior US Patent No. 6,261,822. The examiner states that this is a double patenting rejection and takes the position that the hyperthermostable protease of SEQ ID NO:3 recited in claim 1 of '822 is a functional equivalent of either SEQ ID NO:1 or 5.

This rejection is obviated by the amendments to claims 1 and 2. As discussed above and as can be seen from the amino acid sequence alignments of SEQ ID NOs:1 and 3 attached hereto, the % sequence identity between SEQ ID NO:1 and 3 is 78%. This means that claim 1 of '822 cannot anticipate the functional equivalents of hyperthermostable protease of SEQ ID NO:1 in which only a single amino acid residue up to 5% of the amino acid residues are changed.

With regard to the hyperthermostable protease of SEQ ID NO:5, which is hybrid of SEQ ID NOs:1 and 3, where residues 133-261 of SEQ ID NO:5 are residues 1-129 of SEQ ID NO:3 and

residues 262-659 of SEQ ID NO:5 are residues 262-659 of SEQ ID NO:1. Accordingly, claim 1 of '822 also cannot anticipate the recited functional equivalents of the hyperthermostable protease of SEQ ID NO:5 because there is much more than a 5% difference in sequence identity between SEQ ID NOs:3 and 5.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /ACY/_____
Allen C. Yun
Registration No. 37,971

ACY:srd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\A\Aoyb\Takakura1B\pto\2007-05-21 AMD.doc

Blast 2 Sequences results

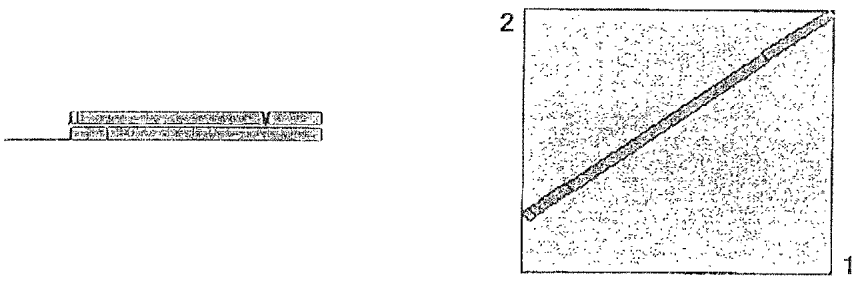
PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.15 [Oct-15-2006]

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.000 wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

Sequence 1: lcl|1_seq_1 SEQ 3
Length = 522 (1 .. 522)

Sequence 2: lcl|2_seq_2 SEQ 1
Length = 659 (1 .. 659)



NOTE:Bitscore and expect value are calculated based on the size of the nr database.

Score = 825 bits (2132), Expect = 0.0
Identities = 407/520 (78%), Positives = 443/520 (85%), Gaps = 7/520 (1%)

```
Query  9    SAAQVMATYVWN-LGYDGSGITIGIIDTGIDASHPDLQGKVIGWVDFVNGRSYPYDDHGH  67
            S +Q+ A  VWN LGYDGSG+ + I+DTGIDA+HPDL+GKVIGW D VNGRS PYDD GH
Sbjct  141  SVSQIGADTVWNSLGYDGSGVVVAIVDTGIDANHPDLKGKVIGWYDAVNGRSTPYDDQGH  200

Query  68   GTHVASIAAGTGAASNGKYKGMAPGAKLAGIKVLGADGSGSISTIIKGVEWAVDNKDKYG  127
            GTHVA I AGTG+  N +Y G+APGAKL G+KVLGADGSGS+STII GV+W V NKDKYG
Sbjct  201  GTHVAGIVAGTGSV-NSQYIGVAPGAKLVGVKVLGADGSGSVSTIIAGVDWVVQNKDKYG  259

Query  128  IKVINLSLGSSQSSDGTDALSQAVNAAWDAGLVVVVAAGNSGPNKYTIGSPAAASKVITV  187
            I+VINLSLGSSQSSDGTD+LSQAVN AWDAG+VV VAAGNSGPN YTIGSPAAASKVITV
Sbjct  260  IRVINLSLGSSQSSDGTDSLSQAVNNAWDAGIVVCVAAGNSGPNTYTVGSPAAASKVITV  319

Query  188  GAVDKYDVITSFSSRGPTADGRLKPEVVAPGNWIIAARASGTSMGQPINDYYTAAPGTSM  247
            GAVD  D I SFSSRGPTADGRLKPEVVAPG  IIA RASGTSMG PINDYYT A GTSM
Sbjct  320  GAVDSNDNIASFSSRGPTADGRLKPEVVAPGVDIIAPRASGTSMGTPINDYYTKASGTSM  379

Query  248  ATPHVAGIAALLLQAHPSWTPDKVKTALIETADIVKPDEIADIAYGAGRVNAYKAINYDN  307
            ATPHV+G+ AL+LQAHPSWTPDKVKTALIETADIV P EIADIAYGAGRVN YKAI YD+
Sbjct  380  ATPHVSGVGALILQAHPSWTPDKVKTALIETADIVAPKEIADIAYGAGRVNVYKAIKYDD  439

Query  308  YAKLVFTGYVANKGSQTHQFVISGASFVTATLYWDNANSDLDLYLYDPNGNQVDYSYTAY  367
            YAKL FTG VA+KGS TH F +SGA+FVTATLYWD  +SD+DLYLYDPNGN+VDYSYTAY
Sbjct  440  YAKLTFTGSVADKGSATHTFDVSGATFVTATLYWDTGSSDIDLYLYDPNGNEVDYSYTAY  499
```

```
Query  368  YGFEKVGYYNPTDGTWTIKVVSYSGSANYQVDVVSDGSLSQ-----PGSSPSPQPEPTVD  422
            YGFEKVGYYNPT GTWT+KVVSY G+ANYQVDVVSDGSLSQ     P  +P+P P PT D
Sbjct  500  YGFEKVGYYNPTAGTWTVKVVSYKGAANYQVDVVSDGSLSQSGGGNPNPNPNPNPTPTTD  559

Query  423  AKTFQXSDHYYYDRSDTFTMTVNSGATKITGDLVFDTSYHDLDLYLYDPNQKLVDRSESP  482
             +TF  S + Y+D SDTFTM VNSGATKITGDL FDTSY+DLDLYLYDPN  LVDRS S
Sbjct  560  TQTFTGSVNDYWDTSDTFTMNVNSGATKITGDLTFDTSYNDLDLYLYDPNGNLVDRSTSS  619

Query  483  NSYEHVEYLTPAPGTWYFLVYAYYTYGWAYYELTAKVYYG  522
            NSYEHVEY  PAPGTW FLVYAY TYGWA Y+L A VYYG
Sbjct  620  NSYEHVEYANPAPGTWTFLVYAYSTYGWADYQLKAVVYYG  659
```

```
CPU time:      0.03 user secs.          0.00 sys. secs      0.03 total secs.

Lambda     K      H
   0.313    0.132    0.395

Gapped
Lambda     K      H
   0.267   0.0410    0.140

Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Sequences: 1
Number of Hits to DB: 3575
Number of extensions: 2009
Number of successful extensions: 7
Number of sequences better than 10.0: 1
Number of HSP's gapped: 1
Number of HSP's successfully gapped: 1
Length of query: 522
Length of database: 1,660,314,297
Length adjustment: 140
Effective length of query: 382
Effective length of database: 1,660,314,157
Effective search space: 634240007974
Effective search space used: 634240007974
Neighboring words threshold: 9
X1: 16 ( 7.2 bits)
X2: 129 (49.7 bits)
X3:  `9 (49.7 bits)
S1: 42 (21.9 bits)
S2: 82 (36.2 bits)
```